Rejections Under 35 U.S.C. §103(a)

Claims 1-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the Dhodapkar et al. reference taken with the Nicholson et al. reference.

In the previous Office Action of August 18, 2000, the Examiner stated that the Dhodapkar et al. reference shows applicant's compound temozolomide (TMZ) being "administered p.o. at doses ranging from 50 mg/m^2/day to 250 mg/m^2/day for 5 days, every 4 wks." (lines 8 and 9 of abstract). The Examiner noted that the Nicholson et al. reference teaches administering TMZ "orally for 5 days, with subsequent courses administered every 21 to 28 days. . . . Dose levels tested included 100, 150, 180, 215, 245 and 260 mg/m^2 daily" (lines 5-7 of abstracts). The Examiner also noted that the reference(s) do not teach all the steps in the claims, including the rest period of 5-14 days. The Examiner concluded that one skilled in this art would be motivated to modify the resting period and closing period in the absence of a side-by-side comparison.

In this present Final Office Action, the Examiner maintains the rejection of claims 1-11 under 35 U.S.C. 103(a) as being unpatentable over Dhodopkar et al. and Nicholson et al. reference as previously set forth in Paper No. 3, page 2 (i.e., the August 18, 2000 Office Action). Presently, the Examiner states the Applicant's remarks are noted but stated that a "showing of two rest times is needed. (The prior art vs. claimed rest times)."

Applicant respectfully traverses the outstanding rejection and presents the following comments regarding the rest times for pending claims 1-11. Applicant respectfully suggests that a prima facie case of obviousness cannot be established based on applicant's previous comments of record and those comments below.

As previously stated, Applicant's invention differs from the prior art in that the rest period of applicant's claim 1 is 5 –14 days, well below the rest period taught by the Dhodapkar and Nicholson articles. Further, applicant respectfully reiterates that its dose schedule of 40 to 150 mg/m^2/day followed by the rest period of 5 to 14 days is non-obvious in light of the cited articles. Further as previously stated, the **maximum** dosing range of claim 1 is 150

mg/m^2/day, a **maximum** dose level well below that of the maximum dose levels of the Dhodapkar and Nicholson articles

Applicant respectfully points out to the Examiner that the shorter rest periods in combination with the lower dosing range maximum allows the present invention to dose a patient "for at least two cycles of a cyclical dosing schedule" (see claim 1).

The present invention's nonobviousness resides in its shorter rest periods combined with its double dosing regiment per dose cycle and its generally lower maximum dose levels. The longer rest periods and significantly higher maximum dose levels of both Dhodapkar and Nicholson teach away from the shorter rest period and lower **maximum** dose of the present invention. Further, the present invention is not specifically limited to cancer treatments requiring pre-treatment with nitrosurea or prior cranio-spinal irradiation treatment combined with TMZ, as described by Dhodapkar and Nicholson, respectively. The Examiner has acknowledged that Dhodapkar and Nicholson do not teach all the steps in the claims, including the rest period of 5-14 days. Nowhere in either Dhodapkar or Nicholson is there any suggestion of the lower resting periods or the decreased **maximum** dosage level of the present invention. Applicant further points out that its cyclical dosing schedule is not limited to 5 days, unlike Dhodapkar and Nicholson. Further, Dhodapkar and Nicholson administer temozolomide only once per dose cycle, accompanied by a longer rest period. Applicant's invention allows for a double dosing of temozolomide per dose cycle, which allows for a shorter rest period as well as a lower maximum dose level. Applicant's invention allows for a higher total dose per month, which is a desirable goal when treating patient's afflicted with cancer. There is no teaching or suggestion of using the method of the pending invention.

Further, applicant respectfully suggests that there is no motivation to modify the resting period and closing period of Dhodapkar and Nicholson that would render claims 1-11 obvious. The art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *See In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2

U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). As stated previously, both publications teach a cycle where temozolomide is given once during the cycle followed by a three-week rest period. Neither reference teaches the claimed dose schedule and the Applicant has not been shown from either publication, where there would be any motivation to modify either Dhodapkar's or Nicholson's dose schedule to render claims 1-11 obvious. Applicant respectfully requests the Examiner to highlight in the publications, any motivation to modify the respective dose schedules.

Applicant respectfully suggests that the proposed modification of the Dhodapkar and Nicholson reference would not have a reasonable expectation of success from the vantagepoint of the skilled artisan at the time the invention was made, i.e. a hindsight analysis is not allowed. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Applicant respectfully suggests as there is no teaching of the method of claims 1-11 (or a motivation to modify, see above) in the cited references, only the use of impermissible hindsight would render these claims obvious in light of Dhodapkar and Nicholson.

Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q.2d 494, 496 (C.C.P.A. 1970). As stated previously by the Examiner, Dhodapkar and Nicholson do not teach all the steps in the claims, including but not limited too, the rest period of 5 to 14 days. Therefore, applicant submits that the present invention is not obvious over the methods disclosed in Dhodapkar, Nicholson or combination thereof. Reconsideration and withdrawal of this ground of rejection is urged.

Claims 12-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the CA 2,184,545 (CA '545) patent. The Examiner notes that CA 2,184,545 teaches a capsule containing 5 mg of temozolomide (See Abstracts last three lines).

Applicant respectfully traverses the rejection and presents the following comments. Applicant respectfully submits that claims 12-19 are not obvious over CA '545. However, in an effort to expedite the prosecution of

this application, applicant has canceled claims 12-19, thus rendering this ground of rejection moot. Withdrawal of this ground of rejection is urged.

In view of the foregoing, applicant submits that the application, as amended, is in condition for allowance and courteously solicits a Notice of Allowance.

The Examiner is requested to call the undersigned attorney on any matter connected with this application.

Respectfully submitted,
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